Severe Persistent Therapeutics: The New Landscape

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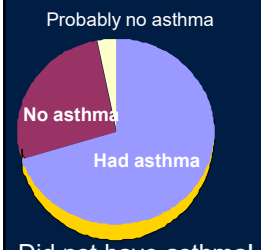
Disclosures

- Professor of Medicine; National Jewish Health; University of Colorado, Denver
- Astra Zeneca: Speaker, advisor
- GSK: Advisor, research
- Sanofi/Regeneron: Advisor
- "Opinions and assertions herein are not representative of either entity but are of my own opinion"

Step #1. Make sure the patient has asthma



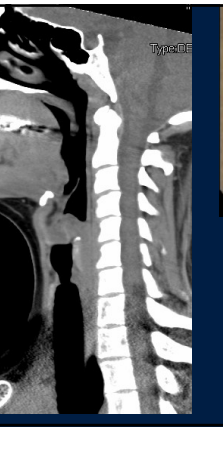
- 150 pts referred to difficult asthma clinic at NJH
  - Extensive evaluation
- Similar to results from Canada in milder asthma (random dialing approach evaluating ~500 "asthmatics" *Aaron et al, CMJ 2008*

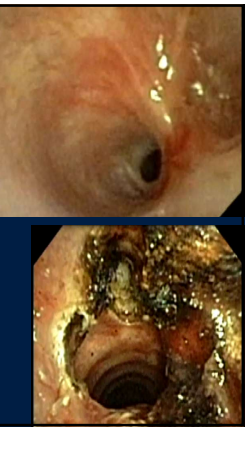
Differential Dx Of Wheezing

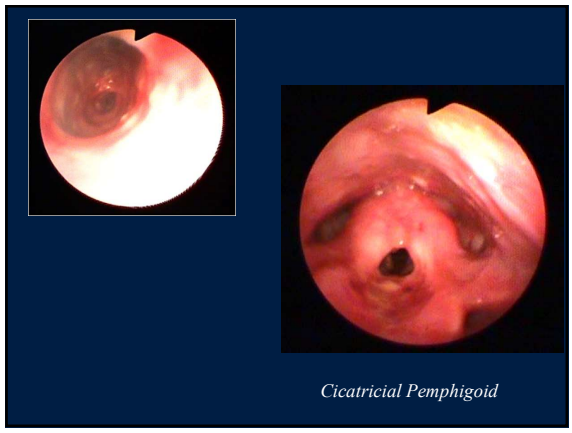
- "Asthma"
- VCD
- ABPA
- Chronic Eosinophilic Pneumonia
- Airway Tumors
- Bronchostenosis/TBM/DAC
- CHF
- Infection
- TB
- Tonsils
- Foreign body
- Goiter
- Post polio syndrome
- COPD
- PE
- Fixed lesions

Spiro

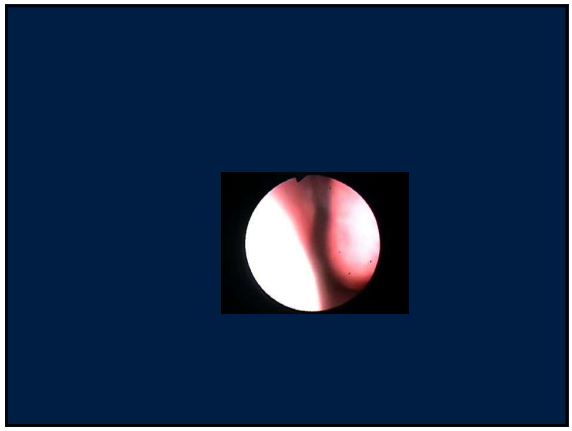
	LLN	Pred	Best	%Pred	Act1	Act2	Act3	Act4	Act5	Act6	Act7	Act8	Act9	Act10
FVC	3.23	3.95	4.40	111.5	3.97	4.35	4.40							
FEV 1	2.83	3.44	1.96	57.1	2.16	1.82	1.96							
FEV1/F	77	86	45		54	42	45							
PEF	5.27	7.06	2.10	29.7	2.31	2.09	2.10							
F25/75	2.51	3.80	1.62	42.6	1.86	1.17	1.62							
PIF		4.30	1.34	31.1	1.34	1.45	1.41							
FE/FIF		124	130	104.7	157	90	149							
FET			5.21		3.66	5.60	5.21							
VBe/FV			1.63		0.87	1.28	1.63							

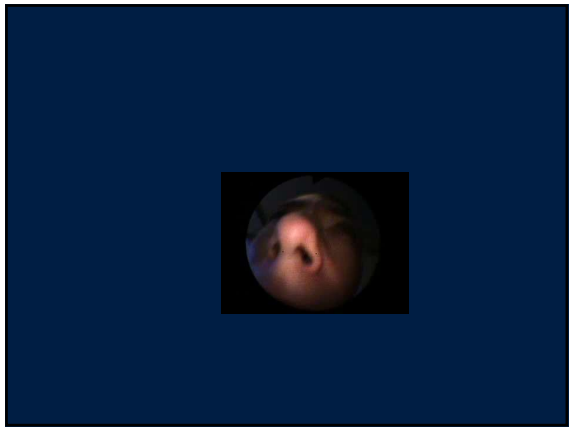




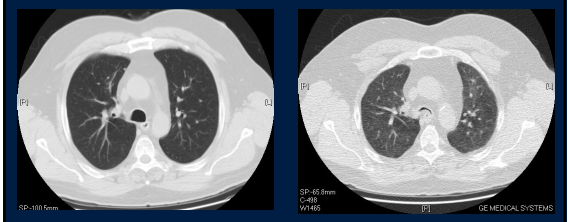


Cicatricial Pemphigoid





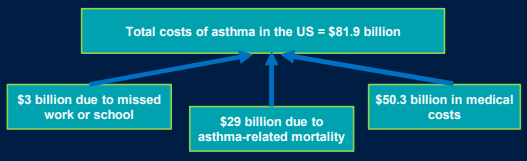
Dyspnea at Rest and with Exertion/ "Severe Asthma"



End-Inspiratory *Dynamic Expiratory*

Dynamic Expiratory CT Severe Tracheomalacia

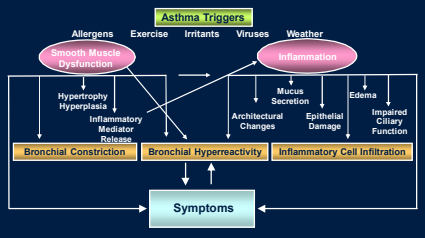
Asthma Cost to Society 2008-2013



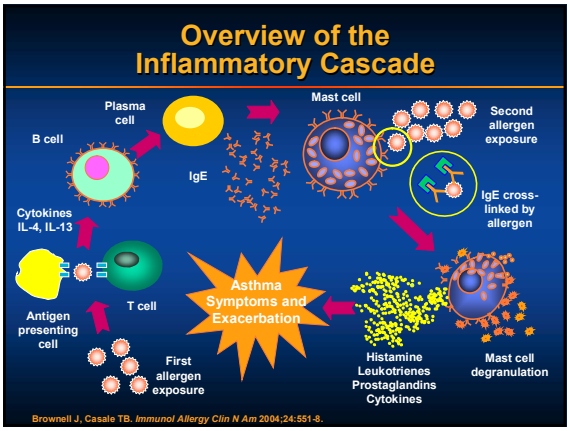
Severe asthmatics represent ~10 % of adults with asthma but incur >60% of costs

Nurmagambetov T et al. Annals ATS. 2018;15(3):348-356.
Israel et al; NEJM. 2017;377:965-976.

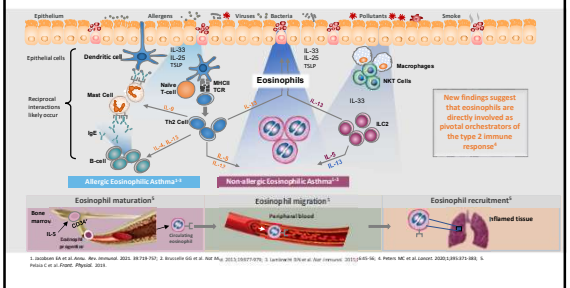
Mechanisms of Asthma Leading to Symptoms



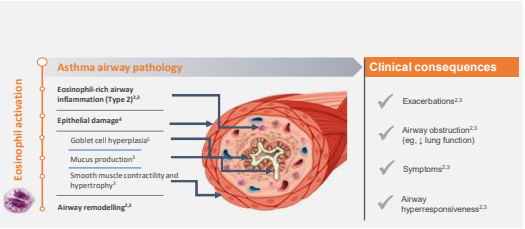
Adapted from Cretices. *Adv Stud Med*. 2002;2:499-503.



Eosinophils Can Have Reciprocal Interactions With Other Immune Cells to Perpetuate Chronic Inflammation[1]



Eosinophilic Inflammation Is Central to the Key Pathological Features and Clinical Consequences of Asthma



EOS = eosinophils.

1. Peters MC et al. *Lancet*. 2020;395:375-383. 2. The Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2021; 3. Israel E et al. *N Engl J Med*. 2017;377:965-976; 4. Gandhi NA et al. *Nat Rev Drug Discov*. 2016;15:35-50; 5. McBrien et al. *Front Med*. 2017;4.

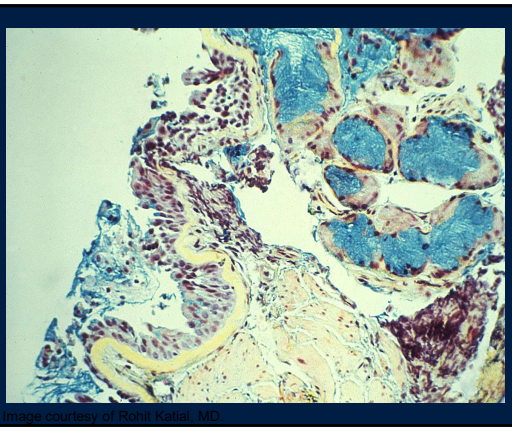
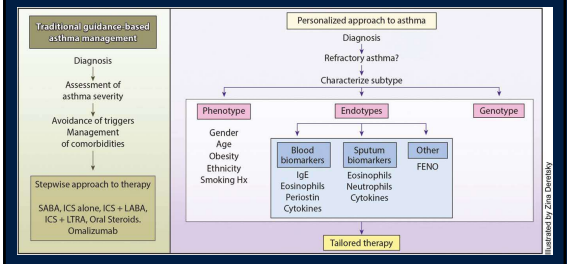


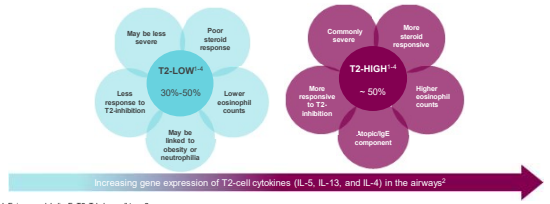
Image courtesy of Rohit Katial, MD

Traditional and Personalized Approach to Asthma Therapy



Dunn RM and Wechsler ME. Clinical Pharmacology and Therapeutics 2015; 97(1): 55-65

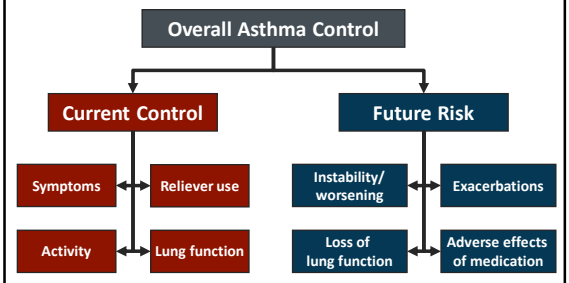
T2-Low and T2-High: Examples of Asthma Phenotypes[1,2]



IgE=immunoglobulin E; T2=T-helper cell type 2.

1. Fahy JV. *Nat Rev Immunol.* 2015;15(1):57-65.
2. Woodruff PG, et al. *Am J Respir Crit Care Med.* 2009;180:388-395.
3. Wenzel SE. *Nat. Med.* 2012;18(5):716-725.
4. Peters MC, et al. *J Allergy Clin Immunol.* 2014;133(2):388-394.

Goals of Asthma Treatment



NHLBI website.
Taylor DR, et al. *Eur Respir J*. 2008;32:545-554.

Goals of Asthma Therapy

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/work missed
- Maintain (near) normal pulmonary function
- Minimal use of inhaled short-acting beta$_2$-agonist
- Minimal or no adverse effects from medications

Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2022.
NIH, NHLBI. May 2003 (reprint). NIH Publication No. 02-5075.

Asthma Therapy Through the Ages

G. Cardano
- Diet
- Exercise
- Sleep
- No feathers

T. Willis
- Fetid gums
- Musk
- Vitrioloic ether

J. Floyer
- Gill
- Hyssop
- Syrup of sulphur
- Bleeding

W. Osler
- Atropine
- Morphine
- Chloroform
- Lobelia

1500s 1600s 1700s 1800s

- Amyl nitrate
- Asthma cigarettes

Asthma Therapy – 1800s

Asthma Therapy in the 1900s

- Adrenaline
- Methyl xanthines

- Oral steroids
- β-agonists

- Long-acting β_2-agonists
- Leukotriene modifiers

1900-30s 1940s 1950s 1970s 1990s

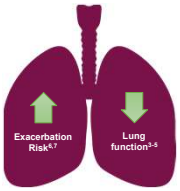
- Systemic steroids (ACTH)

- Cromones
- Inhaled steroids
- β_2-selective agonists

Biologics

Biomarkers

Summary: Increased Eosinophils in Asthma

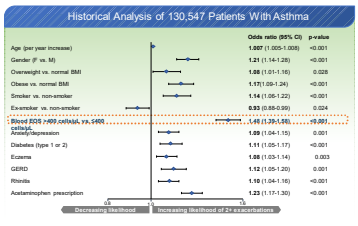


Elevated eosinophils were correlated with:

- Increased asthma severity[1,2]
- Worsening lung function[3-5]
- Increased risk of exacerbations[6,7]
- Increased rates of hospitalizations and ED visits[6]

1. Bousquet J et al. *N Engl J Med.* 1990;323:1033-1039; 2. Louis R et al. *Am J Respir Crit Care Med.* 2000;161:9-16; 3. Broekema M et al. *Respir Med.* 2010;104:1254-1262; 4. Woodruff PG et al. *J Allergy Clin Immunol.* 2009;358:753-758; 5. McGrath KW et al. *Am J Respir Crit Care Med.* 2012;185:612-619; 6. Zeiger RS et al. *J Allergy Clin Immunol Pract.* 2014;2:741-750; 7. Price D et al. *J Asthma Allergy.* 2014;9:1-12.

Increased Eosinophils in Asthma: Major Risk Factor for Exacerbations



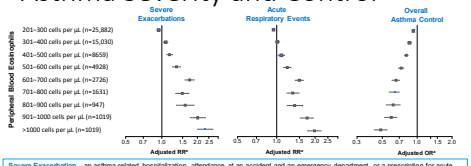
Blood eosinophil >400 cells/µL:

- **Single best predictor of multiple exacerbations**
- **↑ likelihood of ≥2 exacerbations by 1.5-fold**

Adapted from Price D et al. *J Asthma Allergy.* 2016;9:1-12.

BMI = body mass index; CI = confidence interval; EOS = eosinophils; F = female; GERD = gastroesophageal reflux disease; M = male.

Peripheral Blood Eosinophil Levels Have Been Correlated With Both Asthma Severity and Control



Severe Exacerbation - an asthma-related hospitalization, attendance at an accident and an emergency department, or a prescription for acute oral OCS

Acute Respiratory Event - defined more broadly as an asthma-related hospital attendance or admission, or accident and an emergency department attendance, a prescription for acute OCS, or prescription for antibiotics in conjunction with an asthma-related primary care consultation

Overall Asthma Control - the absence of any acute respiratory event (as defined above) or asthma-related outpatient department visit with an average daily dose of 200 µg or less of salbutamol or 500 µg or less of terbutaline

*Data from medical records of patients with asthma who were aged 12-60 years and had 2 years of continuous records, including 1 year before (baseline) and 1 year after (outcome) their most recent eosinophil count. Patients were assigned to 9 eosinophil count categories and were compared with a reference category of 200 cells/µL (n=66,407). Data adjusted for age, gender, body mass index, smoking status, and Charlson comorbidity index score.

OCS = oral corticosteroids; OR = odds ratio; RR = rate ratio.

Price DB et al. *Lancet Respir Med*. 2015;3:849-858.

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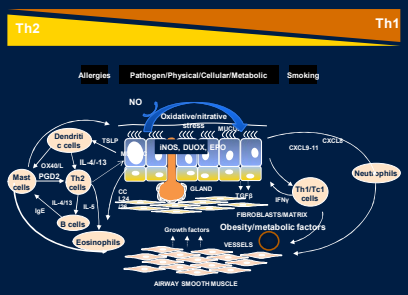
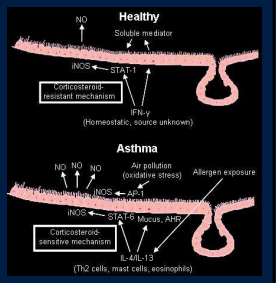
Pathobiology may involve multiple different immune/cellular pathways



Nitric Oxide (No) Production[1,2]

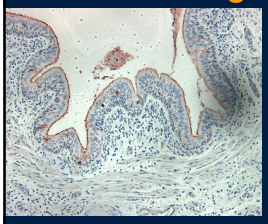
- NO—endogenous regulatory molecule
- Synthesis regulated by family of enzymes—NO synthases (NOS)
- Inducible NOS-derived NO is predominantly produced in bronchial wall epithelial cells
- Exhaled NO levels increase during Th2 (allergic) inflammation—often correlate with eosinophilic inflammation



AP, activator protein; iNOS, inducible nitric oxide synthase; IL, interleukin; IFN-γ, interferon-gamma; STAT, signal transducer and activator of transcription;

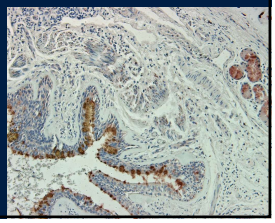
1. Yates. *Immunol Cell Biol*. 2001;79(2):178-190. 2. Alving et al. *Eur Respir Mon*. 2010;49:1-31.

iNOS Staining

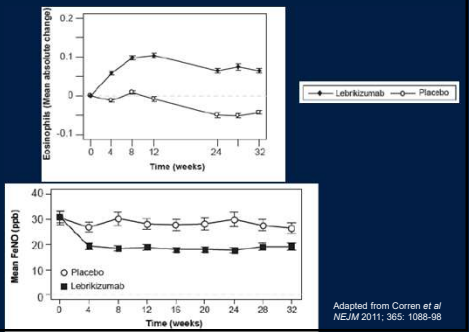


iNOS Stain in a Normal Subject

iNOS Stain in a Severe Asthmatic

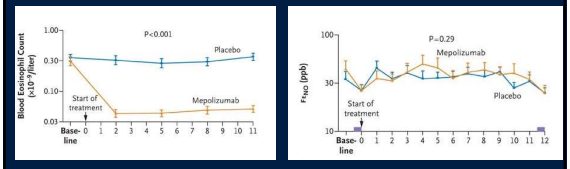


FeNO and Eosinophils After Anti-IL-13 Treatment



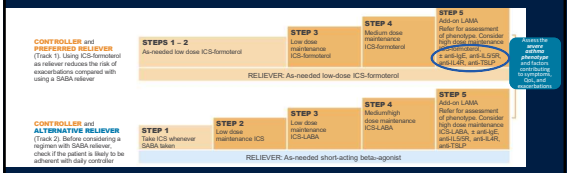
Adapted from Corren *et al* *NEJM* 2011; 365: 1088-98

FeNO and Eosinophils After Anti-IL-5 Treatment



Adapted from Haldar et al; NEJM 2009; 360: 973-84

GINA 2022 Guidelines: Add Biologics at Step 5



Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022. Available from: www.ginasthma.org

Important Th2 Biologic Targets

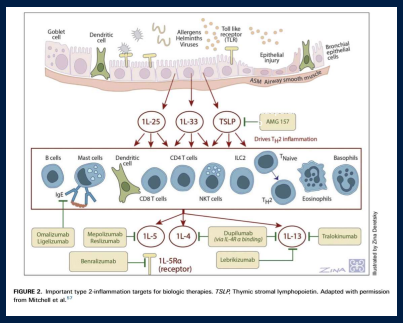


FIGURE 2. Important type 2 inflammation targets for biologic therapies. *TSLP,* Thymic stromal lymphopoietin. Adapted with permission from Mitchell et al.[17]

Katial et al. JACI: In Practice 2017. 5(2): S1-S14.

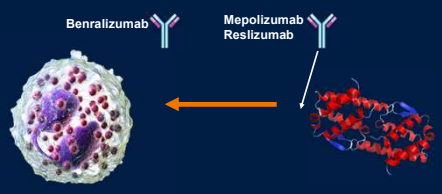
Anti-IL5

Mepolizumab
Reslizumab

IL5R

benralizumab

The Targets: IL-5 or Eosinophils (IL-5Rα)



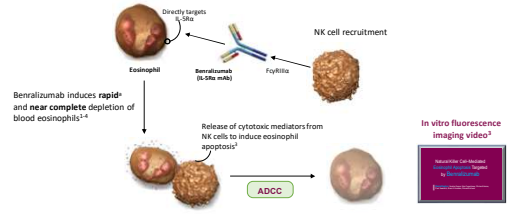
Eosinophil

- Raised levels are present in 40–60% of asthmatics.
- Release toxins that promote airway inflammation in asthmatic patients

IL-5

- Principal eosinophilic regulatory cytokine
- Involved in the maturation, differentiation, survival, and activation of eosinophils

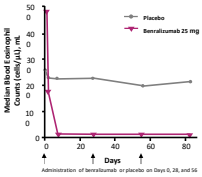
Benralizumab Mechanism of Action: *Enhanced Antibody-Dependent Cell- Mediated Cytotoxicity*



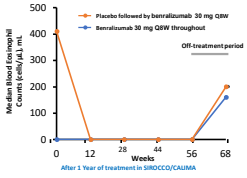
[a]Benralizumab induces eosinophil apoptosis within 6 hours in vitro;[3] blood eosinophils were depleted within 24 hours in a phase 1 study[2]
ADCC = antibody-dependent cell-mediated cytotoxicity; ECS = eosinophil; Fc = fragment crystallizable region; IL-5Rα = interleukin 5 receptor alpha; mAb = monoclonal antibody; MOA = mechanism of action; NK = natural killer.
1. Kolbeck R et al. *J Allergy Clin Immunol*. 2010;125:1344-1353. 2. Laviolette M et al. *J Allergy Clin Immunol* 2013;132:1086-1096. 3. Dagher R et al. Oral presentation presented at International Eosinophil Society 10th Biennial Symposium; 19-23 July 2017; Gothenburg, Sweden; 4. Tan LD et al. *J Asthma Allergy*. 2016;9:71-81.

Rapid and Sustained Blood Eosinophil Depletion With Benralizumab

Phase IIa (CP197) study in patients with mild to moderate asthma[1]



Phase III (BORA) extension study of SIROCCO and CALIMA patients (≥300 cells/μL)[2,a]



[a]The median EOS count at Week 68 was 10 cells/μL, Q4W/Q4W; 10 cells/μL, PBO/Q4W; 160 cells/μL, Q8W/Q8W, 200 cells/μl, PBO/Q8W; Q8W last dose at Week 48, Q4W last dose on Week 52.
EOS = eosinophil; MOA = mechanism of action; Q4W = every 4 weeks; Q8W = every 8 week (first 3 doses Q4W).
1. Pham TH et al. *Respir Med*. 2016;111:21-29. 2. Busse WW et al. Supplementary appendix. *Lancet Resp Med*. 2019;7:46-59.

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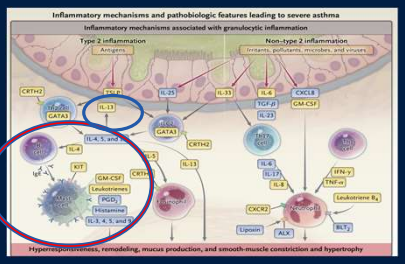
Anti IL-5 Improves Outcomes in Eosinophilic Asthma

- Mepolizumab, benralizumab, reslizumab
  - Reduce Eosinophils
  - Reduce Exacerbations
  - Improve Lung Function
  - Improve Quality of Life
  - Facilitate Corticosteroid Withdrawal

Biologics can target IL4 and IL13



GM-CSF=granulocyte-macrophage colony-stimulating factor; Ig=immunoglobulin; IL=interleukin; ILC2=innate lymphoid cell type 2; NKT cells=natural killer T cells; T_H17=T helper cell 17; T_H2=T helper type 2 cell; TSLP=thymic stromal lymphopoietin.

From Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. Drazen JM, ed. *N Engl J Med*. 377(10):965-976. Copyright© 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

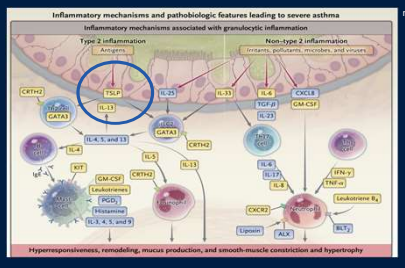
Broader Blockade of Type 2 Cytokines IL-4 and IL-13 Improves Outcomes

- Dupilumab
  - Targets IL-4 receptor alpha
  - Prevents IL-4 and IL-13 from binding to IL-13 receptor
- Works downstream via jak-stat dependent pathways to
  - Prevent IL-4 mediated production of IgE
  - Prevent IL-13 mediated eNO and mucus production
  - Prevent IL-4 and IL-13 mediated trafficking of eosinophils into the tissue

Dupilumab Anti IL-4/13

- Reduces Exacerbations
  - Improves Lung Function
  - Improves Quality of Life
  - Facilitate Corticosteroid Withdrawal
- Also approved for atopic dermatitis, chronic rhinosinusitis, eosinophilic esophagitis, prurigo nodularis

What about blocking epithelial alarmins?



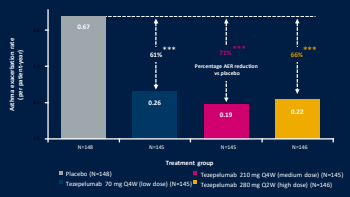
GM-CSF=granulocyte-macrophage colony-stimulating factor; Ig=immunoglobulin; IL=interleukin; ILC2=innate lymphoid cell type 2; NKT cells=natural killer T cells; T_H17=T helper cell 17; T_H2=T helper type 2 cell; TSLP=thymic stromal lymphopoietin.

Tezepelumab Targets TSLP and Blocks Inflammation from the Top of the Cascade

- Tezepelumab – human monoclonal antibody that binds to TSLP, specifically blocking it from interacting with its receptor
- Has potential to inhibit multiple downstream inflammatory pathways and enact broad effects on airway inflammation

Tezepelumab treatment reduced exacerbations vs placebo

Significant reduction in annualised AER for all tezepelumab treatment groups compared with placebo; P<0.001



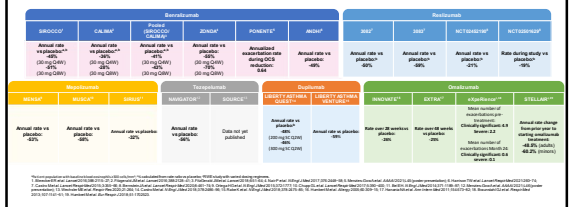
Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377(10):936-946.

An overview of biologic therapies used in inflammatory disorders

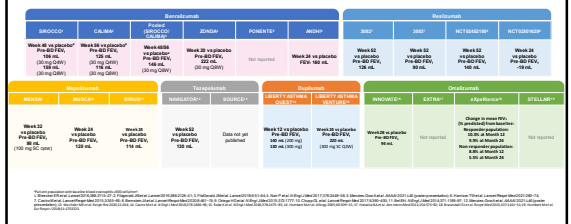
	Benralizumab[1,2]	Reslizumab[2,3]	Mepolizumab[2,4]	Tezepelumab[5]	Dupilumab[2,6]	Omalizumab[2,7]
Mode of action	Humanized mAb to IL-5Rα Recruits NK cells to eosinophils via IL-5Rα that directly induce apoptosis via enhanced ADCC; it also depletes with IL-5 signalling	Humanized mAb to IL-5 Binds to and inhibits IL-5 ligation to IL-5Rα, suppressing IL-5 signalling	Humanized mAb to IL-5 Binds to and inhibits IL-5 ligation to IL-5Rα, suppressing IL-5 signalling	Humanized mAb to TSLP Targets and blocks TSLP from interacting with its receptor complex (TSLPR/IL-7Rα), suppressing inflammatory signalling	Humanized mAb to IL-4Rα Binds to IL-4Rα and inhibits both IL-4 and IL-13 signalling pathways	Humanized mAb to IgE Binds free IgE, inhibiting IgE interactions with the high-affinity IgE receptors (FcεRI), suppressing inflammatory signalling
Administration	Subcutaneous	Intravenous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous
Indications	Add-on therapy for severe eosinophilic asthma (≥12 years of age)[a]	Add-on therapy for severe eosinophilic asthma (≥18 years of age)	Add-on therapy for moderate-to-severe eosinophilic asthma (≥6 years of age) HES (≥12 years of age) EGPA (adults)	Not yet approved	Add-on therapy for severe eosinophilic asthma (≥12 years of age) Severe CRSwNP (adults) AD (≥6 years of age)	Add-on therapy for severe allergic asthma (≥6 years of age) Severe CRSwNP (adults) CSU (≥12 years of age)
Approval dates	Asthma: 2017 (USA), 2018 (EU)	Asthma: 2016 (USA and EU)	Asthma: 2015 (USA), 2019 (EU) HES: 2020 (USA) EGPA: 2017 (USA)	NA	Asthma: 2018 (USA), 2019 (EU) CRSwNP: 2019 (USA and EU) AD: 2020 (USA and EU)	Asthma: 2003 (USA), 2005 (EU) CRSwNP: 2020 (USA and EU) CSU: 2014 (USA and EU)

[a]Given by EU-approved dose in ≥18 years of age.

Exacerbation rates for all biologics (overall population)



Lung function for all biologics (overall population)



Summary

- "Guideline" guided treatment is not optimal in at least 50% of patients
- Step 3 and above assessment of role of TH2 mechanism to guide therapy
- Recognition and treatment of co-morbidities

Summary

- Biologics are currently directed to TH2 pathways
- Biomarkers currently being studied most extensively are Th2 based in relation to current therapeutics

Summary

- Type 2 or T2 high asthma can be eosinophilic, allergic, or mixed
- Type 2 cytokines IL-4, IL-13, and IL-5 lead to airway remodeling, nitric oxide production, smooth muscle contractility, and eosinophil activation and recruitment
- Non type 2 or T2 low asthma can be neutrophilic or paucigranulocytic
- Neutrophilic asthma has poorer response to corticosteroids, higher associations with fixed airflow obstruction
- Paucigranulocytic asthma demonstrates uncoupling of airway structural changes and remodeling from inflammation